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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,229	01/16/2007	Ozlem Tureci	VOS-203	4951

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Olson & Cepuritis, LTD.
20 NORTH WACKER DRIVE
36TH FLOOR
CHICAGO, IL 60606

EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,229	TURECI ET AL.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *116 and 118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *116 and 118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed November 20, 2009 in response to the Office Action of June 23, 2009, is acknowledged and has been entered. Claims 116 and 118 are pending and being examined. Claims 1-115 and 117 are canceled.

New Rejections

(based on new considerations)

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 116 and 118 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim s 116 and 118 recite the limitation "**the level of a nucleic acid**". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 116 and 118 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for **a method for diagnosing melanoma in a**

patient, the method comprising detecting the presence of a nucleic acid comprising SEQ ID NO:1 in a skin tissue sample from the patient, does not reasonably provide enablement for a method for diagnosing melanoma in a patient comprising detecting any level of a nucleic acid comprising SEQ ID NO:1 or for determining regression, course or onset of melanoma, comprising detecting any level of a nucleic acid comprising SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims (see section 2 of the previous Office Action).

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method for diagnosing cancer in a patient, the method comprising detecting the level of a nucleic acid comprising SEQ ID NO:1 in a tissue sample from the patient and a method for determining regression, course, or onset of cancer in a patient, the method comprising detecting the level of a nucleic acid comprising SEQ ID NO:1 in a tissue sample from the patient.

The specification discloses identifying nucleic acid sequences of tumor associated antigens differentially expressed in tumors and discloses SEQ ID NO:1 (p. 4, lines 23-28; p. 5, line 5). The specification discloses that SEQ ID NO:1 mRNA was expressed in melanoma tissue samples but not detected in normal skin tissue samples (Figures 1 and 2; Example 3). The specification contemplates that the regression, course, or onset of a disease including cancer can be determined by monitoring a sample from a patient with cancer for abnormal expression of tumor associated antigens, or by determining expression in the sample at a first and second time point to determine the course of disease (p. 16, lines 5-39).

One cannot extrapolate the disclosure of the specification to the scope of the claims because the specification does not provide guidance or examples for diagnosing melanoma comprising detecting **any level of SEQ ID NO:1** in skin samples. The specification discloses only a nexus between the detection of SEQ ID NO:1 mRNA expression in skin tissue samples and the diagnosis of melanoma. The specification fails to provide a nexus between the diagnosis of melanoma based on any levels of

SEQ ID NO:1, including levels of zero. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Given the teaching of the art, without a validated nexus provided between a level of SEQ ID NO:1, including zero

levels, in skin and the presence of melanoma, one of skill in the art could not predictably use the claimed level as a diagnostic agent to diagnose melanoma. *Given the teaching of the specification, a level of zero for SEQ ID NO:1 would not predictably diagnose melanoma, there fore melanoma cannot be diagnosed based on detecting a level of zero for the nucleic acid comprising SEQ ID NO:1, as broadly encompassed by the claims.*

Finally, one cannot extrapolate the disclosure of the specification to the scope of the claims because the specification does not provide guidance or examples for any methods of determining **regression, course, or onset** of melanoma. The specification does not provide a nexus between any levels of SEQ ID NO:1 and a predictable determination of regression, course of cancer, or onset of cancer. The specification discloses only the detection of SEQ ID NO:1 mRNA in melanoma tissue sample and the absence of SEQ ID NO:1 mRNA in normal skin samples. Following the teaching of Tockman et al above, one of skill in the art could not reasonably extrapolate this data to the enablement of methods for determining regression, course, or onset of melanoma because the specification does not exemplify or identify any measurements of levels in SEQ ID NO:1 that predictably determine an regression, course, or onset of cancer. The single measurements of mRNA expression in each melanoma sample of Figures 1 and 2 do not indicate what stage cancer the patients have and do not determine cancer outcome, hence one of skill in the art could not determine if the cancer is regressing, what course the cancer is taking, and if it is the onset or beginning of cancer.

Therefore, in view of the state of the art, the quantity of experimentation necessary, the breadth of the claims, lack of guidance in the specification, and the absence of working examples for diagnosing melanoma and determining the regression, course, and onset of cancer based on any level of SEQ ID NO:1 in any tissue, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

Response to Relevant Arguments

4. Applicants argue that the Office Action indicates that the application is enabling for diagnosis of melanoma by detecting expression of SEQ ID NO:1 in a skin sample from a patient as set forth in present claim 116.

The arguments have been considered but are not found persuasive. Examiner has clarified the enablement for claim 116 as being enabled for diagnosing melanoma in a patient comprising detecting *presence* of a nucleic acid comprising SEQ ID NO:1 in a skin tissue sample from the patient, hence the presence of SEQ ID NO:1 must be detected for diagnoses, rather than detecting any level of SEQ ID NO:1 including zero level. The claims as currently constituted comprise detecting zero levels of SEQ ID NO:1 for diagnosis and are not enabled for the reasons set forth above.

5. With regards to claim 118, Applicants argue that the level of skill in the medical and oncological arts is very high. Applicants argue that one of ordinary skill in the art

would logically conclude from the teaching of the present application and from the common meaning of the word itself that "diagnosis" encompasses *inter alia* assessment of regression, course, and onset of the disease. If the presence of the marker in a skin tissue sample is considered diagnostic for melanoma, then the absence of the marker after treatment indicates a regression, and the presence of the marker after a previous negative tissue test would indicate onset of melanoma. Onset, regression, and the existence of the disease state *per se* all relate to the "course" of the disease.

The arguments have been considered but are not found persuasive. Applicants opine that if the presence of the marker in a skin tissue sample is considered diagnostic for melanoma, then the absence of the marker after treatment indicates a regression, and the presence of the marker after a previous negative tissue test would indicate onset of melanoma, however, the specification does not provide any examples or teach levels of SEQ ID NO:1 that predictably determine regression, onset, or the course of melanoma in a patient, and a high quantity of experimentation would be required to determine what effects treatment have on SEQ ID NO:1 and what levels indicate regression, onset, or course of melanoma in a patient. Examiner disagrees that "diagnosis" encompasses assessment of regression, course, and onset of the disease, and the scope each of these assessments is different. For example, a patient "diagnosed" with melanoma based on the presence of SEQ ID NO:1 would not be necessarily or simultaneously determined to have "regression," "onset," or have their "course" of melanoma determined, and the specification does not teach what level of SEQ ID NO:1 would indicate such an assessment. The specification is not enabling for

determining regression, onset, or the course of melanoma in a patient for the reasons set forth above.

6. All other rejections recited in the Office Action mailed June 23, 2009 are hereby withdrawn.

7. **Conclusion:** No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Primary Examiner, Art Unit 1642